(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 February 2003 (27.02.2003)

PCT

(10) International Publication Number
WO 03/016310 A1

(51) International Patent Classification[7]: C07D 471/14, A61K 31/435, C07D 491/14, A61P 1/04, A61K 31/35 // (C07D 471/14, 235:00, 221:00, 221:00)

(21) International Application Number: PCT/EP02/08498

(22) International Filing Date: 31 July 2002 (31.07.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
01118674.9 3 August 2001 (03.08.2001) EP

(71) Applicant *(for all designated States except US)*: **ALTANA PHARMA AG** [DE/DE]; Byk-Gulden-Str. 2, 78467 Konstanz (DE).

(72) Inventors: **BUHR, Wilm**; Zum Kirchenwald 7, 78465 Konstanz (DE). **SIMON, Wolfgang-Alexander**; Schubertstrasse 17, 78464 Konstanz (DE). **POSTIUS, Stefan**; Austrasse 4b, 78467 Konstanz (DE). **KROMER, Wolfgang**; Hinterhauserstr. 5, 78464 Konstanz (DE). **STURM, Ernst**; Bohlstrasse 9, 78465 Konstanz (DE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **SENN-BILFINGER, Jörg** [DE/DE]; Säntisstrasse 7, 78464 Konstanz (DE). **ZIMMERMANN, Peter, Jan** [DE/DE]; Zum Lerchental 43/1, 78315 Radolfzell (DE).

(74) Common Representative: **ALTANA PHARMA AG**; Byk-Gulden-Strasse 2, 78467 Konstanz (DE).

(81) Designated States *(national)*: AE, AL, AU, BA, BR, CA, CN, CO, CU, DZ, EC, GE, HR, HU, ID, IL, IN, IS, JP, KR, LT, LV, MA, MK, MX, NO, NZ, PH, PL, RO, SG, SI, TN, UA, US, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AL, AU, BA, BR, CA, CN, CO, CU, DZ, EC, GE, HR, HU, ID, IL, IN, IS, JP, KR, LT, LV, MA, MK, MX, NO, NZ, PH, PL, RO, SG, SI, TN, UA, VN, YU, ZA, ZW, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR)*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ALKYL-SUBSTITUTED IMIDAZOPYRIDINES FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS

(57) Abstract: Compounds of the formula 1, in which the substituents and symbols are as defined in the description are suitable for pre-venting and treating gastrointestinal disorders.

WO 03/016310 A1

ALKYL-SUBSTITUTED IMIDAZOPYRIDINES FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS

Field of application of the invention

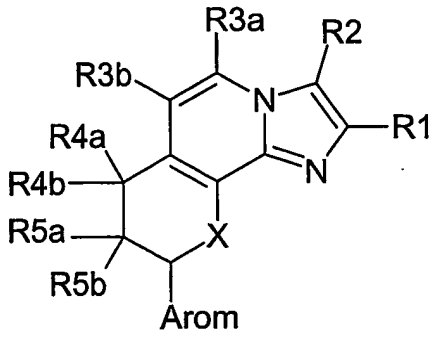
The invention relates to novel compounds which are used in the pharmaceutical industry as active compounds for preparing medicaments.

Prior art

US Patent 4,468,400 describes tricyclic imidazo[1,2-a]pyridines having different ring systems fused to the imidazopyridine skeleton, which compounds are said to be suitable for treating peptic ulcer disorders. The International Patent Applications WO95/27714, WO 98/42707, WO 98/54188, WO 00/17200, WO 00/26217, WO 00/63211, WO01/72754 and WO01/72757 disclose inter alia tricyclic imidazopyridine derivatives having a very specific substitution pattern, which compounds are likewise said to be suitable for treating gastrointestinal disorders. - Kaminski et al., J. Med. Chem. **1991**, *34*, 533-541 and **1997**, *40*, 427-436 describe the synthesis of imidazo[1,2-a]pyridines and their use as antiulcer agents.

Description of the invention

The invention provides compounds of the formula 1



(1)

where

R1 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxycarbonyl, 2-4C-alkenyl, 2-4C-alkynyl, fluoro-1-4C-alkyl or hydroxy-1-4C-alkyl,

R2 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxycarbonyl, hydroxy-1-4C-alkyl, halogen, 2-4C-alkenyl, 2-4C-alkynyl, fluoro-1-4C-alkyl or cyanomethyl,

R3a is hydrogen, halogen, fluoro-1-4C-alkyl, 1-4C-alkyl, 2-4C-alkenyl, 2-4C-alkynyl, 1-4C-alkoxy, carboxyl, 1-4C-alkoxycarbonyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkyl, fluoro-1-4C-alkoxy-1-4C-alkyl or the radical -CO-NR31R32,

R3b is hydrogen, halogen, fluoro-1-4C-alkyl, 1-4C-alkyl, 2-4C-alkenyl, 2-4C-alkynyl, 1-4C-alkoxy, carboxyl, 1-4C-alkoxycarbonyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkyl, fluoro-1-4C-alkoxy-1-4C-alkyl or the radical -CO-NR31R32,

where

R31 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl and

R32 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl,

or where

R31 and R32 together and including the nitrogen atom to which they are attached form a pyrrolidino, piperidino or morpholino radical,

one of the substituents R4a and R4b is hydrogen and the other is the radical R41,

where

R41 is 1-7C-alkyl, 2-7C-alkenyl, 3-7C-cycloalkyl, 1-4C-alkoxy-1-4C-alkyl, cyano-1-4C-alkyl, phenyl or phenyl-1-4C-alkyl,

one of the substituents R5a and R5b is hydrogen and the other is hydroxyl, 1-4C-alkoxy, oxo-substituted 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkyl-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, 3-7C-cycloalkoxy-1-4C-alkoxy, 3-7C-cycloalkyl-1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkylcarbonyloxy, fully or predominantly halogen-substituted 1-4C-alkoxy or the radical R51,

where

R51 is a radical which, under physiological conditions, forms a hydroxyl group,

Arom is a R8-, R9-, R10- and R11-substituted mono- or bicyclic aromatic radical selected from the group consisting of phenyl, naphthyl, pyrrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, indolyl, benzimidazolyl, furanyl (furyl), benzofuranyl (benzofuryl), thiophenyl (thienyl), benzothiophenyl (benzothienyl), thiazolyl, isoxazolyl, pyridinyl, pyrimidinyl, quinolinyl and isoquinolinyl,

where

R8 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy, 2-4C-alkenyloxy, 1-4C-alkylcarbonyl, carboxyl, 1-4C-alkoxycarbonyl, carboxy-1-4C-alkyl, 1-4C-alkoxycarbonyl-1-4C-alkyl, halogen, hydroxyl, aryl, aryl-1-4C-alkyl, aryloxy, aryl-1-4C-alkoxy, trifluoromethyl, nitro, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or sulfonyl,

R9 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxyl,

R10 is hydrogen, 1-4C-alkyl or halogen and

R11 is hydrogen, 1-4C-alkyl or halogen,

where

aryl is phenyl or substituted phenyl having one, two or three identical or different substituents from the group consisting of 1-4C-alkyl, 1-4C-alkoxy, carboxyl, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl, nitro, trifluoromethoxy, hydroxyl and cyano,

X is O (oxygen) or NH,

and their salts.

1-4C-Alkyl denotes straight-chain or branched alkyl radicals having 1 to 4 carbon atoms. Examples which may be mentioned are the butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl, ethyl and methyl radicals.

3-7C-Cycloalkyl denotes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, among which cyclopropyl, cyclobutyl and cyclopentyl are preferred.

3-7C-Cycloalkyl-1-4C-alkyl denotes one of the abovementioned 1-4C-alkyl radicals which is substituted by one of the abovementioned 3-7C-cycloalkyl radicals. Examples which may be mentioned are the cyclopropylmethyl, the cyclohexylmethyl and the cyclohexylethyl radicals.

1-4C-Alkoxy denotes radicals which, in addition to the oxygen atom, contain a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Examples which may be mentioned are the butoxy, isobutoxy, sec-butoxy, tert-butoxy, propoxy, isopropoxy and preferably the ethoxy and methoxy radicals.

1-4C-Alkoxy-1-4C-alkyl denotes one of the abovementioned 1-4C-alkyl radicals which is substituted by one of the abovementioned 1-4C-alkoxy radicals. Examples which may be mentioned are the methoxymethyl, the methoxyethyl and the butoxyethyl radicals.

1-4C-Alkoxycarbonyl (-CO-1-4C-alkoxy) denotes a carbonyl group to which is attached one of the abovementioned 1-4C-alkoxy radicals. Examples which may be mentioned are the methoxycarbonyl (CH_3O-C(O)-) and the ethoxycarbonyl (CH_3CH_2O-C(O)-) radicals.

2-4C-Alkenyl denotes straight-chain or branched alkenyl radicals having 2 to 4 carbon atoms. Examples which may be mentioned are the 2-butenyl, 3-butenyl, 1-propenyl and the 2-propenyl (allyl) radicals.

2-4C-Alkynyl denotes straight-chain or branched alkynyl radicals having 2 to 4 carbon atoms. Examples which may be mentioned are the 2-butynyl, the 3-butynyl and, preferably, the 2-propynyl (propargyl radicals).

Fluoro-1-4C-alkyl denotes one of the abovementioned 1-4C-alkyl radicals which is substituted by one or more fluorine atoms. An example which may be mentioned is the trifluoromethyl radical.

Hydroxy-1-4C-alkyl denotes abovementioned 1-4C-alkyl radicals which are substituted by a hydroxyl group. Examples which may be mentioned are the hydroxymethyl, the 2-hydroxyethyl and the 3-hydroxypropyl radicals.

For the purpose of the invention, halogen is bromine, chlorine and fluorine.

1-4C-Alkoxy-1-4C-alkoxy denotes one of the abovementioned 1-4C-alkoxy radicals which is substituted by a further 1-4C-alkoxy radical. Examples which may be mentioned are the radicals 2-(methoxy)ethoxy (CH_3-O-CH_2-CH_2-O-) and 2-(ethoxy)ethoxy (CH_3-CH_2-O-CH_2-CH_2-O-).

1-4C-Alkoxy-1-4C-alkoxy-1-4C-alkyl denotes one of the abovementioned 1-4C-alkoxy-1-4C-alkyl radicals which is substituted by one of the abovementioned 1-4C-alkoxy radicals. An example which may be mentioned is the radical 2-(methoxy)ethoxymethyl (CH_3-O-CH_2-CH_2-O-CH_2-).

Fluoro-1-4C-alkoxy-1-4C-alkyl denotes one of the abovementioned 1-4C-alkyl radicals which is substituted by a fluoro-1-4C-alkoxy radical. Here, fluoro-1-4C-alkoxy denotes one of the abovementioned 1-4C-alkoxy radicals which is fully or predominantly substituted by fluorine. Examples of fully or predominantly fluorine-substituted 1-4C-alkoxy which may be mentioned are the 1,1,1,3,3,3-hexafluoro-2-propoxy, the 2-trifluoromethyl-2-propoxy, the 1,1,1-trifluoro-2-propoxy, the perfluoro-tert-butoxy, the 2,2,3,3,4,4,4-heptafluoro-1-butoxy, the 4,4,4-trifluoro-1-butoxy, the 2,2,3,3,3-pentafluoropropoxy, the perfluoroethoxy, the 1,2,2-trifluoroethoxy, in particular the 1,1,2,2-tetrafluoroethoxy, the 2,2,2-trifluoroethoxy, the trifluoromethoxy and preferably the difluoromethoxy radicals.

1-7C-Alkyl denotes straight-chain or branched alkyl radicals having 1 to 7 carbon atoms. Examples which may be mentioned are the heptyl, isoheptyl-(5-methylhexyl), hexyl, isohexyl-(4-methylpentyl), neohexyl-(3,3-dimethylbutyl), pentyl, isopentyl-(3-methylbutyl), neopentyl-(2,2-dimethylpropyl), butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl, ethyl and methyl radicals.

Oxo-substituted 1-4C-alkoxy denotes a 1-4C-alkoxy group which, instead of a methylene group, contains a carbonyl group. An example which may be mentioned is the 2-oxopropoxy group.

3-7C-Cycloalkoxy denotes cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy and cycloheptyloxy, among which cyclopropyloxy, cyclobutyloxy and cyclopentyloxy are preferred.

3-7C-Cycloalkyl-1-4C-alkoxy denotes one of the abovmentioned 1-4C-alkoxy radicals which is substituted by one of the abovementioned 3-7C-cycloalkyl radicals. Examples which may be mentioned are the cyclopropylmethoxy, the cyclobutylmethoxy and the cyclohexylethoxy radicals.

3-7C-Cycloalkoxy-1-4C-alkoxy denotes one of the abovementioned 1-4C-alkoxy radicals which is substituted by one of the abovementioned 3-7C-cycloalkoxy radicals. Examples which may be mentioned are the cyclopropoxymethoxy, the cyclobutoxymethoxy and the cyclohexyloxyethoxy radicals.

3-7C-Cycloalkyl-1-4C-alkoxy-1-4C-alkoxy denotes one of the abovementioned 1-4C-alkoxy radicals which is substituted by one of the abovementioned 3-7C-cycloalkyl-1-4C-alkoxy

radicals. Examples which may be mentioned are the cyclopropylmethoxyethoxy, the cyclobutylmethoxyethoxy and the cyclohexylethoxyethoxy radicals.

1-4C-Alkylcarbonyl denotes a radical which, in addition to the carbonyl group, contains one of the abovementioned 1-4C-alkyl radicals. An example which may be mentioned is the acetyl radical.

1-4C-Alkylcarbonyloxy denotes a 1-4C-alkylcarbonyl group which is attached to an oxygen atom. An example which may be mentioned is the acetoxy radical (CH_3CO-O-).

Fully or predominantely halogen-substituted 1-4C-alkoxy which may be mentioned are primarily chlorine- and/or, in particular, fluorine-substituted 1-4C-alkoxy radicals. Examples of halogen-substituted 1-4C-alkoxy which may be mentioned are the 2,2,2-trichloroethoxy, the hexachloroisopropoxy, the pentachloroisopropoxy, the 1,1,1-trichloro-3,3,3-trifluoro-2-propoxy, the 1,1,1-trichloro-2-methyl-2-propoxy, the 1,1,1-trichloro-2-propoxy, the 3-bromo-1,1,1-trifluoro-2-propoxy, the 3-bromo-1,1,1-trifluoro-2-butoxy, the 4-bromo-3,3,4,4-tetrafluoro-1-butoxy, the chlorodifluoromethoxy, the 1,1,1,3,3,3-hexafluoro-2-propoxy, the 2-trifluoromethyl-2-propoxy, the 1,1,1-trifluoro-2-propoxy, the perfluoro-tert-butoxy, the 2,2,3,3,4,4,4-heptafluoro-1-butoxy, the 4,4,4-trifluoro-1-butoxy, the 2,2,3,3,3-pentafluoropropoxy, the perfluoroethoxy, the 1,2,2-trifluoroethoxy, in particular the 1,1,2,2-tetrafluoroethoxy, the 2,2,2-trifluoroethoxy, the trifluoromethoxy and preferably the difluoromethoxy radicals.

A radical R51 which forms a hydroxyl group under physiological conditions is to be understood as meaning a radical -OR' from which, in the body of a human or animal, the group R' is cleaved off hydrolytically forming the radical –OH and the non-toxic compound R'OH. Thus, the radical R' can also be referred to as a hydroxyl protective group or as a prodrug radical. Such hydroxyl protective groups or prodrug radicals are known, inter alia, from the patent applications and patents DE 4308095, WO 95/14016, EP 694547, WO 95/11884, WO 94/05282 and US 5,432,183. Radicals R' having the general structure -C(O)R, -C(O)NRaRb, -P(O)ORaORb or -$S(O)_2$OR, where R, Ra and Rb denote any organic radicals or, if appropriate, hydrogen, may be mentioned by way of example.

In the context of the invention, exemplary radicals R' which are to be particularly mentioned are the groups

-C(O)-NR12R13,

-C(O)-Alk-NR12R13,

-C(O)-Alk-C(O)-NR12R13,

-$P(O)(OH)_2$,

-$S(O)_2$NR12R13,

-C(O)-R12,

-C(O)-C_6H_3R14R15,

-C(O)-OR12,

-C(O)-Alk-C(O)-R12,

-C(O)-Alk-C(O)-OR12,
-C(O)-C(O)-R12,
-C(O)-C(O)-OR12 and
-CH_2-OR12,
where
Alk is 1-7C-alkylene,
R12 is hydrogen, 1-7C-alkyl or halogen-, carboxyl-, hydroxyl-, sulfo- (-SO_3H), sulfamoyl- (-SO_2NH_2), carbamoyl- (-$CONH_2$), 1-4C-alkoxy- or 1-4C-alkoxycarbonyl-substituted 1-4C-alkyl,
R13 is hydrogen or 1-4C-alkyl,
R14 is hydrogen, halogen, nitro, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, 1-4C-alkoxycarbonylamino, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or trifluoromethyl and
R15 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy.

1-7C-Alkylene denotes straight-chain or branched 1-7C-alkylene radicals, for example the methylene (-CH_2-), ethylene (-CH_2CH_2-), trimethylene (-$CH_2CH_2CH_2$-), tetramethylene (-$CH_2CH_2CH_2CH_2$-), 1,2-dimethylethylene [-$CH(CH_3)$-$CH(CH_3)$-], 1,1-dimethylethylene [-$C(CH_3)_2$-CH_2-], 2,2-dimethylethylene [-CH_2-$C(CH_3)_2$-], isopropylidene [-$C(CH_3)_2$-], 1-methylethylene [-$CH(CH_3)$-CH_2-], pentamethylene (-$CH_2CH_2CH_2CH_2CH_2$-), hexamethylene (-$CH_2CH_2CH_2CH_2CH_2CH_2$-) and heptamethylene (-$CH_2CH_2CH_2CH_2CH_2CH_2CH_2$-) radicals.

In this context, the groups -C(O)-$N(CH_3)_2$, -C(O)-$N(C_2H_5)_2$, -C(O)-NHC_2H_5, -C(O)-$CH_2CH_2NH_2$, -C(O)-$(CH_2)_3NH_2$, -C(O)-$C(CH_3)_2NH_2$, -C(O)-$CH_2N(CH_3)_2$, -C(O)-$CH(NH_2)$-$CH(CH_3)_2$, -C(O)-$CH(NH_2)CH(CH_3)C_2H_5$, -C(O)-$(CH_2)_6C(O)N(CH_3)CH_2CH_2SO_3H$, -$P(O)(OH)_2$, -$S(O)_2NH_2$, -C(O)-H, -C(O)-$C(CH_3)_3$, -C(O)-$CH_2CH_2COOH$, -C(O)-$CH_3$, -C(O)-$C_2H_5$, -C(O)-$C_6H_5$, -C(O)-$C_6H_4$-4-$NO_2$, -C(O)-$C_6H_4$-3-$NO_2$, -C(O)-$C_6H_4$-4-$OCH_3$, -C(O)-$C_6H_4$-4-C(O)-$OCH_3$, -C(O)-$OCH_3$, -C(O)-O-menthyl, -C(O)-CH_2-C(O)-OCH_3, -C(O)-CH_2CH_2-C(O)-OCH_3, -C(O)-C(O)-OCH_3, -C(O)-C(O)-OC_2H_5 and -$CH_2OCH(CH_3)_2$ are to be mentioned as exemplary radicals R' to which particular emphasis is given.

1-4C-Alkoxycarbonylamino denotes an amino radical which is substituted by one of the abovementioned 1-4C-alkoxycarbonyl radicals. Examples which may be mentioned are the ethoxycarbonylamino and the methoxycarbonylamino radicals.

1-4C-Alkoxy-1-4C-alkoxycarbonyl denotes a carbonyl group to which one of the abovementioned 1-4C-alkoxy-1-4C-alkoxy radicals is attached. Examples which may be mentioned are the 2-(methoxy)-ethoxycarbonyl (CH_3-O-CH_2CH_2-O-CO-) and the 2-(ethoxy)ethoxycarbonyl (CH_3CH_2-O-CH_2CH_2-O-CO-) radicals.

1-4C-Alkoxy-1-4C-alkoxycarbonylamino denotes an amino radical which is substituted by one of the abovementioned 1-4C-alkoxy-1-4C-alkoxycarbonyl radicals. Examples which may be mentioned are the 2-(methoxy)ethoxycarbonylamino and the 2-(ethoxy)ethoxycarbonylamino radicals.

2-4C-Alkenyloxy denotes a radical which, in addition to the oxygen atom, contains a 2-4C-alkenyl radical. An example which may be mentioned is the allyloxy radical.

Aryl-1-4C-alkyl denotes an aryl-substituted 1-4C-alkyl radical. An example which may be mentioned is the benzyl radical.

Aryl-1-4C-alkoxy denotes an aryl-substituted 1-4C-alkoxy radical. An example which may be mentioned is the benzyloxy radical.

Mono- or di-1-4C-alkylamino radicals contain, in addition to the nitrogen atom, one or two of the abovementioned 1-4C-alkyl radicals. Preference is given to di-1-4C-alkylamino and in particular to dimethyl-, diethyl- or diisopropylamino.

1-4C-Alkylcarbonylamino denotes an amino group to which a 1-4C-alkylcarbonyl radical is attached. Examples which may be mentioned are the propionylamino ($C_3H_7C(O)NH$-) and the acetylamino (acetamido, $CH_3C(O)NH$-) radicals.

Radicals Arom which may be mentioned are, for example, the following substituents: 4-acetoxyphenyl, 4-acetamidophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3-benzyloxyphenyl, 4-benzyloxyphenyl, 3-benzyloxy-4-methoxyphenyl, 4-benzyloxy-3-methoxyphenyl, 3,5-bis-(trifluoromethyl)phenyl, 4-butoxyphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-chloro-6-fluorophenyl, 3-chloro-4-fluorophenyl, 2-chloro-5-nitrophenyl, 4-chloro-3-nitrophenyl, 3-(4-chloro-phenoxy)phenyl, 2,4-dichlorophenyl, 3,4-difluorophenyl, 2,4-dihydroxyphenyl, 2,6-dimethoxyphenyl, 3,4-dimethoxy-5-hydroxyphenyl, 2,5-dimethylphenyl, 3-ethoxy-4-hydroxyphenyl, 2-fluorophenyl, 4-fluorophenyl, 4-hydroxyphenyl, 2-hydroxy-5-nitrophenyl, 3-methoxy-2-nitrophenyl, 3-nitrophenyl, 2,3,5-trichlorophenyl, 2,4,6-trihydroxyphenyl, 2,3,4-trimethoxyphenyl, 2-hydroxy-1-naphthyl, 2-methoxy-1-naphthyl, 4-methoxy-1-naphthyl, 1-methyl-2-pyrrolyl, 2-pyrrolyl, 3-methyl-2-pyrrolyl, 3,4-dimethyl-2-pyrrolyl, 4-(2-methoxycarbonylethyl)-3-methyl-2-pyrrolyl, 5-ethoxycarbonyl-2,4-dimethyl-3-pyrrolyl, 3,4-dibromo-5-methyl-2-pyrrolyl, 2,5-dimethyl-1-phenyl-3-pyrrolyl, 5-carboxy-3-ethyl-4-methyl-2-pyrrolyl, 3,5-dimethyl-2-pyrrolyl, 2,5-dimethyl-1-(4-trifluoromethylphenyl)-3-pyrrolyl, 1-(2,6-dichloro-4-trifluoromethylphenyl)-2-pyrrolyl, 1-(2-nitrobenzyl)-2-pyrrolyl, 1-(2-fluorophenyl)-2-pyrrolyl, 1-(4-tri-fluoromethoxyphenyl)-2-pyrrolyl, 1-(2-nitrobenzyl)-2-pyrrolyl, 1-(4-ethoxycarbonyl)-2,5-dimethyl-3-pyrrolyl, 5-chloro-1,3-dimethyl-4-pyrazolyl, 5-chloro-1-methyl-3-trifluoromethyl-4-pyrazolyl, 1-(4-chloro-benzyl)-5-pyrazolyl, 1,3-dimethyl-5-(4-chlorophenoxy)-4-pyrazolyl, 1-methyl-3-trifluoromethyl-5-(3-trifluoromethylphenoxy)-4-pyrazolyl, 4-methoxycarbonyl-1-(2,6-dichlorophenyl)-5-pyrazolyl, 5-allyloxy-1-methyl-3-trifluoromethyl-4-pyrazolyl, 5-chloro-1-phenyl-3-trifluoromethyl-4-pyrazolyl, 3,5-dimethyl-1-phenyl-4-imidazolyl, 4-bromo-1-methyl-5-imidazolyl, 2-butylimidazolyl, 1-phenyl-1,2,3-triazol-4-yl, 3-indolyl, 4-indolyl, 7-indolyl, 5-methoxy-3-indolyl, 5-benzyloxy-3-indolyl, 1-benzyl-3-indolyl, 2-(4-chlorophenyl)-3-indolyl, 7-benzyloxy-3-indolyl, 6-benzyloxy-3-indolyl, 2-methyl-5-nitro-3-indolyl, 4,5,6,7-tetrafluoro-3-indolyl, 1-(3,5-difluorobenzyl)-3-indolyl, 1-methyl-2-(4-trifluorophenoxy)-3-indolyl, 1-methyl-2-benzimidazolyl, 5-nitro-2-furyl, 5-hydroxymethyl-2-furyl, 2-furyl, 3-furyl, 5-(2-nitro-4-

trifluoromethylphenyl)-2-furyl, 4-ethoxycarbonyl-5-methyl-2-furyl, 5-(2-trifluoromethoxyphenyl)-2-furyl, 5-(4-methoxy-2-nitrophenyl)-2-furyl, 4-bromo-2-furyl, 5-dimethylamino-2-furyl, 5-bromo-2-furyl, 5-sulfo-2-furyl, 2-benzofuryl, 2-thienyl, 3-thienyl, 3-methyl-2-thienyl, 4-bromo-2-thienyl, 5-bromo-2-thienyl, 5-nitro-2-thienyl, 5-methyl-2-thienyl, 5-(4-methoxyphenyl)-2-thienyl, 4-methyl-2-thienyl, 3-phenoxy-2-thienyl, 5-carboxy-2-thienyl, 2,5-dichloro-3-thienyl, 3-methoxy-2-thienyl, 2-benzothienyl, 3-methyl-2-benzothienyl, 2-bromo-5-chloro-3-benzothienyl, 2-thiazolyl, 2-amino-4-chloro-5-thiazolyl, 2,4-dichloro-5-thiazolyl, 2-diethylamino-5-thiazolyl, 3-methyl-4-nitro-5-isoxazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 6-methyl-2-pyridyl, 3-hydroxy-5-hydroxymethyl-2-methyl-4-pyridyl, 2,6-dichloro-4-pyridyl, 3-chloro-5-trifluoromethyl-2-pyridyl, 4,6-dimethyl-2-pyridyl, 4-(4-chlorophenyl)-3-pyridyl, 2-chloro-5-methoxycarbonyl-6-methyl-4-phenyl-3-pyridyl, 2-chloro-3-pyridyl, 6-(3-trifluoromethylphenoxy)-3-pyridyl, 2-(4-chlorophenoxy)-3-pyridyl, 2,4-dimethoxy-5-pyrimidine, 2-quinolinyl, 3-quinolinyl, 4-quinolinyl, 2-chloro-3-quinolinyl, 2-chloro-6-methoxy-3-quinolinyl, 8-hydroxy-2-quinolinyl and 4-isoquinolinyl.

Suitable salts of compounds of the formula 1 are – depending on the substitution – in particular all acid addition salts. Particular mention may be made of the pharmacologically acceptable salts of the inorganic and organic acids customarily used in pharmacy. Those suitable are water-soluble and water-insoluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulfuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)benzoic acid, butyric acid, sulfosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulfonic acid, methanesulfonic acid or 3-hydroxy-2-naphthoic acid, where the acids are employed in the salt preparation in an equimolar ratio or in a ratio differing therefrom, depending on whether the acid is a mono- or polybasic acid and on which salt is desired.

Pharmacologically unacceptable salts, which can be initially obtained, for example, as process products in the preparation of the compounds according to the invention on an industrial scale, are converted into the pharmacologically acceptable salts by processes known to the person skilled in the art.

It is known to the person skilled in the art that the compounds according to the invention and their salts can, for example when they are isolated in crystalline form, comprise varying amounts of solvents. The invention therefore also embraces all solvates and, in particular, all hydrates of the compounds of the formula 1, and all solvates and, in particular, all hydrates of the salts of the compounds of the formula 1.

The compounds of the formula 1 have centers of chirality in the skeleton in positions 7, 8 and 9. The invention thus provides all feasible stereoisomers in any mixing ratio, including the pure enantiomers, which are the preferred subject matter of the invention.

Compounds which are to be emphasized are those compounds of the formula 1 where

R1 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl, 1-4C-alkoxy-1-4C-alkyl, 2-4C-alkynyl or fluoro-1-4C-alkyl,

R2 is hydrogen, 1-4C-alkyl, halogen, 2-4C-alkenyl, 2-4C-alkynyl or fluoro-1-4C-alkyl,

R3a is hydrogen,

R3b is hydrogen, halogen, 1-4C-alkyl or the radical -CO-NR31R32,

where

R31 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl and

R32 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl,

or where

R31 and R32 together and including the nitrogen atom to which they are attached are a pyrrolidino, piperidino or morpholino radical,

one of the substituents R4a and R4b is hydrogen and the other is the radical R41,

where

R41 is 1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, cyano-1-4C-alkyl or phenyl-1-4C-alkyl,

one of the substituents R5a and R5b is hydrogen and the other is hydroxyl, 1-4C-alkoxy, oxo-substituted 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkyl-1-4C-alkoxy or 1-4C-alkoxy-1-4C-alkoxy,

Arom is a R8-, R9-, R10- and R11-substituted mono- or bicyclic aromatic radical selected from the group consisting of phenyl, furanyl (furyl) and thiophenyl (thienyl),

where

R8 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkylcarbonyl, carboxyl, 1-4C-alkoxycarbonyl, halogen, hydroxyl, trifluoromethyl, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or sulfonyl,

R9 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxyl,

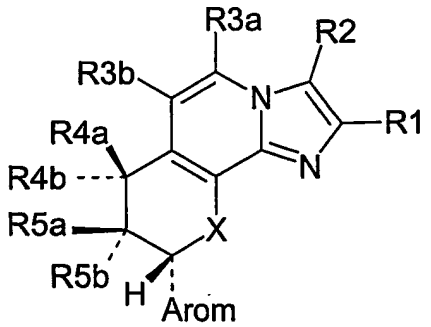
R10 is hydrogen and

R11 is hydrogen,

X is O (oxygen) or NH,

and their salts.

Among the compounds according to the invention, emphasis is given to the optically pure compounds of the formula 1*



(1*)

where the hydrogen atoms in positions 7 and 8 are preferably represented by the substituents R4a and R5b.

Among the compounds of the formula 1*, emphasis is given to those in which

R1 is hydrogen, methyl, cyclopropyl, methoxymethyl or trifluoromethyl,

R2 is hydrogen, methyl, chlorine, bromine, ethynyl or trifluoromethyl,

R3a is hydrogen,

R3b is hydrogen, fluorine, methyl or the radical -CO-N(CH_3)$_2$,

one of the substituents R4a and R4b is hydrogen and the other is the radical R41, where

R41 is 1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, cyano-1-4C-alkyl or phenyl-1-4C-alkyl,

one of the substituents R5a and R5b is hydrogen and the other is hydroxyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, methoxyethoxy, methoxypropoxy, methoxyethoxyethoxy, 2-oxopropoxy, cyclopropyloxy or cyclopropylmethoxy,

Arom is a phenyl radical,

X is O (oxygen) or NH,

and their salts.

Particular emphasis is given to compounds of the formula 1* in which

R1 is 1-4C-alkyl,

R2 is 1-4C-alkyl,

R3a is hydrogen,

R3b is hydrogen,

one of the substituents R4a and R4b is hydrogen and the other is the radical R41, where

R41 is 1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, cyano-1-4C-alkyl, or phenyl-1-4C-alkyl,

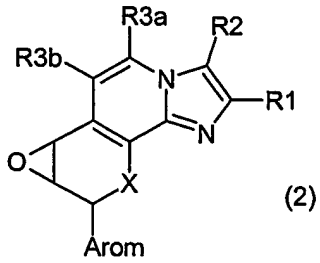
one of the substituents R5a and R5b is hydrogen and the other is hydroxyl,

Arom is a phenyl radical,

X is O (oxygen) or NH,

and their salts.

The compounds of the formula 1 according to the invention can be prepared by reacting compounds M-R41, where R41 is as described above and M is the suitable radical of an organometallic compound, with compounds of the formula Z,



(2)

where R1, R2, R3a, R3b and Arom are as defined above and X is O (oxygen) or N-Prot, where Prot is an amino protective group which has to be cleaved off after the reaction. The reaction is carried out in a manner known per se to the person skilled in the art, depending on which radical R41 is to be

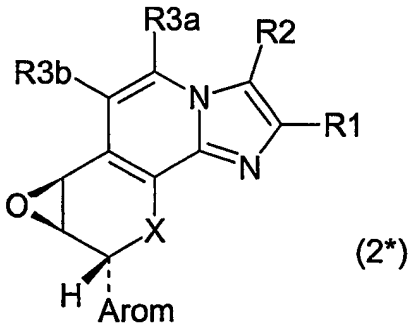
introduced with the use of a customary organometallic compound M-R41 (such as, for example, methyllithium, phenyllithium, 2,2-dimethylvinylmagnesium bromide etc.) in a suitable inert solvent, such as, for example acetonitrile or diethyl ether.

Suitable amino protective groups Prot are, in principle, all protective groups used for protecting amino acids in peptide and protein synthesis or for protecting other amines, for example in the synthesis of alkaloids and nucleotides (see, for example, T. W. Greene and P. G. M. Wuts, Protective groups in organic synthesis, 2nd edition, 1991, John Wiley & Sons, Inc., pages 309-385). Exemplary protective groups which may be mentioned are the radicals 1-4C-alkylcarbonyl (for example acetyl), 1-4C-alkoxycarbonyl (for example butoxycarbonyl), benzyloxycarbonyl or nitrobenzenesulfenyl.

If the desired products are compounds of the formula 1 where X = NH, the amino protective group has to be cleaved off after the reaction of the organometallic compound M-R41 with the compound 2 where X = N-Prot. The amino protective group, for example the acetyl radical, can be cleaved off by heating the reaction product in ethanolamine in the presence of an auxiliary base, such as, for example, potassium carbonate.

The etherification of the hydroxyl group in the 8-position, which may follow, if desired, can be carried out, for example, as described in WO 00/17200. Any introduction of a prodrug radical R' in the 8-position is carried out in an acylation reaction by reaction with compounds of the formula R'-Z in which Z is a suitable leaving group, for example a halogen atom. The reaction is carried out in a manner known per se, preferably in the presence of a suitable auxiliary base.

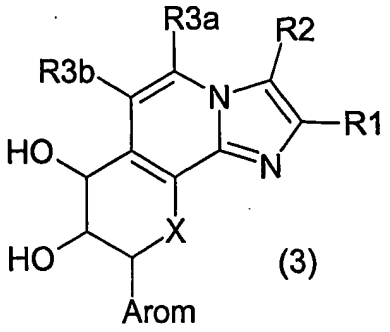
Compounds of the formula 1* which are to be emphasized are obtained by reacting an organometallic compound M-R41 with compounds of the formula 2*



(2*)

in which R1, R2, R3a, R3b and Arom are as defined above and X is O (oxygen) or N-Prot, where Prot is an amino protective group which has to be cleaved off after the reaction.

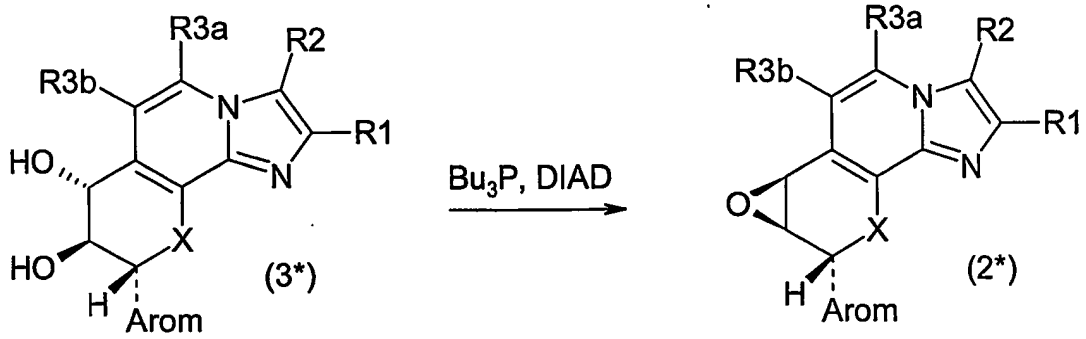
The compounds of the formula 2 in which R1, R2, R3a, R3b and Arom are as defined above and X is O (oxygen) or N-Prot can be prepared from the compounds of the formula 3



(3)

in which R1, R2, R3a, R3b and Arom are as defined above and X is O (oxygen) or N-Prot, as shown in Scheme 1 below in an exemplary manner for the compounds 2* and 3*:

Scheme 1:

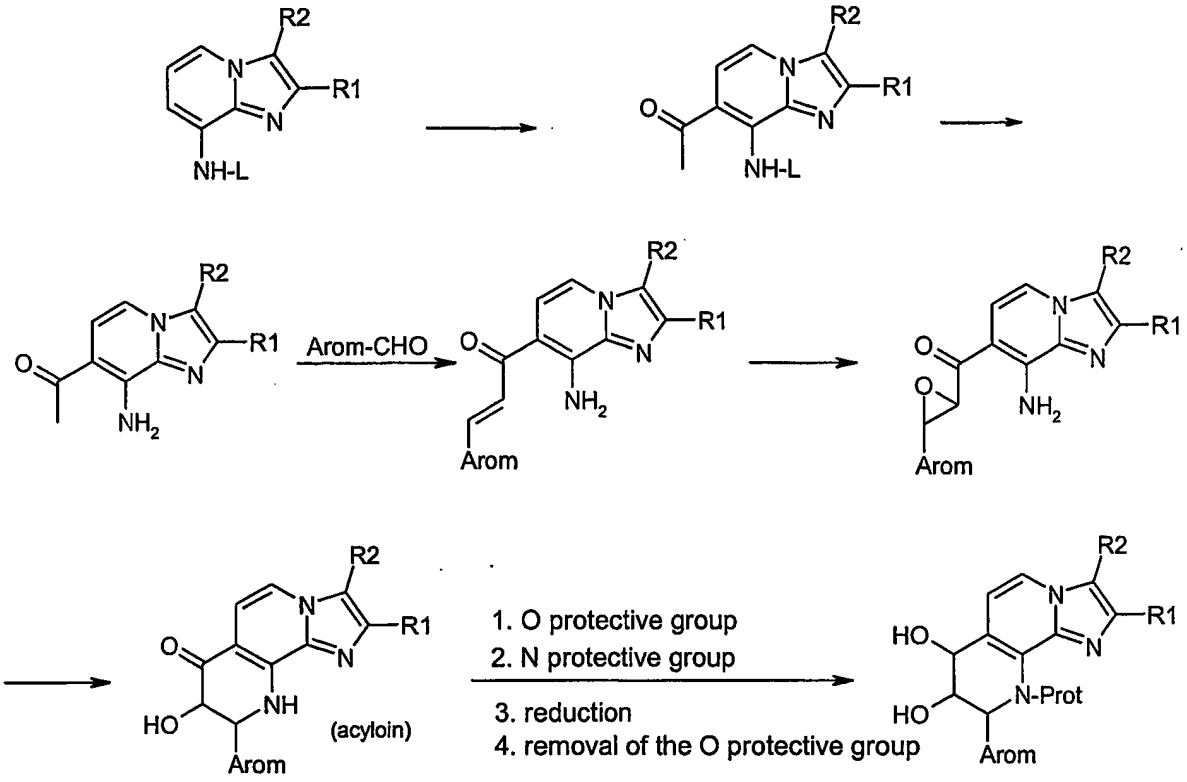


The conversion of the diol into the epoxide according to Scheme 1 is carried out in a manner known per se, for example using tributylphosphine and diisopropyl azodicarboxylate with cooling and under inert conditions (see, for example, J. Voss et al., Synthesis **2001**, 229-234 or R. Mengel et al., Angew. Chem. **1978**, *90*, 725).

Compounds of the formula 3 are known, or they can be prepared as described in an exemplary maner in the examples below, or starting from corresponding starting materials and using analogous process steps (see, for example, WO 98/42707, WO 98/54188, WO 00/17200, WO 00/26217 and WO 00/63211), or as shown quite generally in the schemes below.

Scheme 2:

Preparation of compounds 3 where X = N-Prot, with any substituents R3a and R3b (not shown in the formulae)

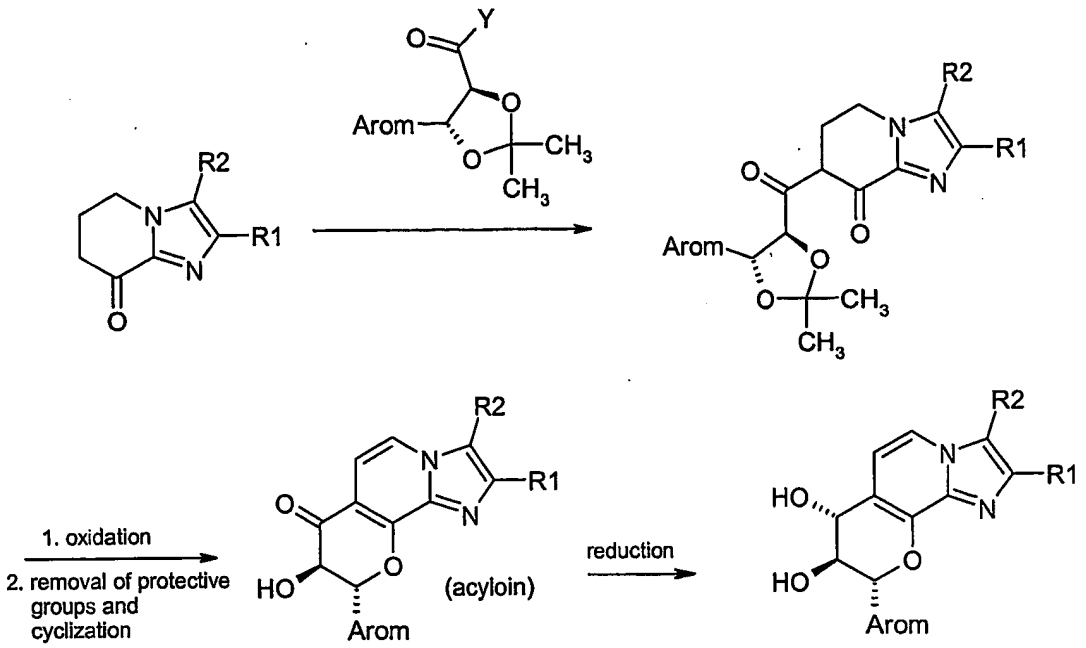


In the above scheme, L denotes any leaving group, for example a pivaloyl group. Introduction of the acetyl group and condensation with the aldehyde Arom-CHO are carried out in a manner known per se. The epoxidation is likewise carried out in a manner known per se, for example using hydrogen peroxide as epoxidizing agent. The introduction of O and N protective groups, the subsequent reduction and the removal of the O protective group that follows are likewise carried out in a manner known per se, for example as described in more detail in the examples below.

The preparation of compounds of the fomula 3, shown by way of example for compounds of the formula 3* where X = O, with any substituents R3a and R3b, is advantageously carried out according to reaction Scheme 3 below.

Scheme 3:

Preparation of compounds 3* where X = O (oxygen), with any substituents R3a and R3b (not shown in the formulae)



In Scheme 3 above, the enantioselective synthesis of a 7,8-diol of the formula 3* where X = O (oxygen) is shown in an exemplary manner. In Scheme 3, group Y is a suitable leaving group, for example a halogen atom, preferably chlorine, or a 1-4C-alkoxy group, preferably methoxy. The acylation is carried out in a manner familiar to the person skilled in the art, preferably using sodium bis(trimethylsilyl)amide or potassium bis(trimethylsilyl)amide, if the leaving group is a chlorine atom.

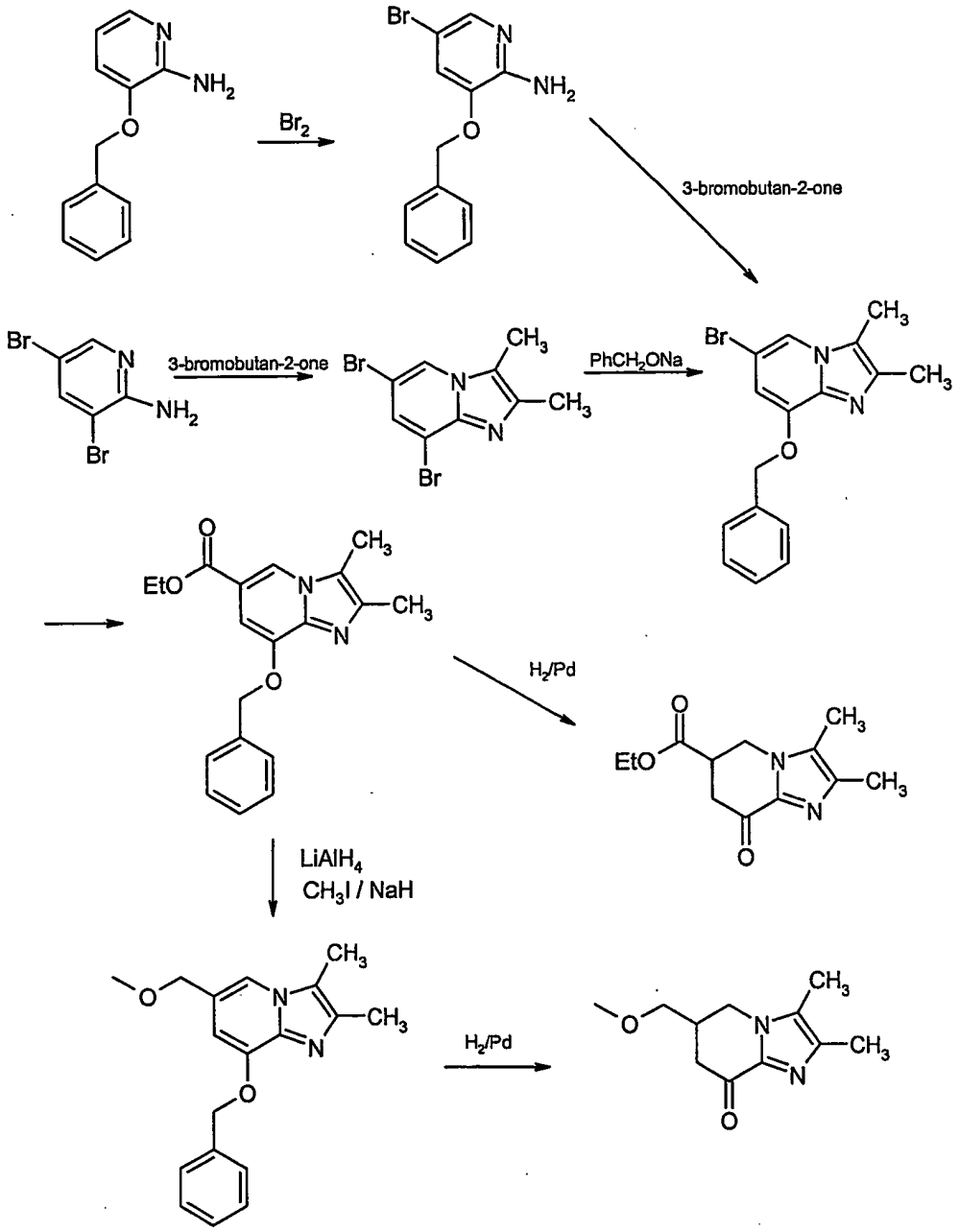
The oxidation that follows after the acylation is likewise carried out under customary conditions using the oxidizing agent chloranil, atmospheric oxygen, 2,3-dichloro-5,6-dicyano-p-benzoquinone or manganese dioxide. For the subsequent removal of protective groups and cyclization, certain conditions have to be met with respect to the auxiliary acid used. The auxiliary acid used is preferably formic acid.

The reduction to the diol is likewise – as in the reduction according to Scheme 2 – carried out under standard conditions (see, for example WO 98/54188), where the reducing agent used is, for example, sodium borohydride, the use of which allows the given 7,8-trans-diol to be obtained in a diastereomeric purity of more than 90%. With respect to the targeted preparation and isolation of the pure enantiomers, reference is made, for example, to the relevant sections in WO 00/17200.

The starting materials shown in Schemes 2 and 3 are known (see, for example, EP-A-299470, Kaminski et al., J. Med. Chem. **1985**, *28*, 876-892, **1989**, *32*, 1686-1700 and **1991**, *34*, 533-541 and Angew. Chem. **1996**, *108*, 589-591), or they can be prepared analogously to the known compounds, for example according to reaction Scheme 4 below.

Scheme 4:

Exemplary preparation of starting materials required for Scheme 3, where R1, R2 = methyl, with various substituents R3b.



The conversion into the 8-benzyloxy-6-bromoimidazopyridines is carried out in a manner familiar to the person skilled in the art. Conversion of the bromine atom into an ethyl ester radical can be effected by various routes, for example using the Heck reaction (with Pd(II), carbon monoxide and ethanol) or by metallation in the 6-position (with lithium or magnesium) and subsequent Grignard reaction. Metallation also offers the option to introduce other desired groups R3b into position 6, for example, fluorine, chlorine or the carboxyl group. Starting from the ester group, it is possible to introduce further desired groups R3b into position 6, for example hydroxy-1-4C-alkyl radicals (in particular the hydroxymethyl radical), by reducing the ester radical with lithium aluminum hydride, or 1-4C-alkoxy-1-4C-alkyl radicals (in particular 1-4C-alkoxymethyl radicals) by subsequent etherification as illustrated in Scheme 4.

The debenzylation/reduction is likewise carried out in a manner known per se, using, for example, hydrogen/Pd(0). If compounds where R3b = -CO-NR31R32 are desired, it is possible to carry out a corresponding derivatization in a manner known per se (conversion of an ester into an amide) at the stage of the 8-benzyloxy-6-ethoxycarbonyl compound or after the debenzylation/reduction, or alternatively also at a later stage, for example at the acyloin stage (see Schemes 2 and 3).

Starting materials with various substituents R1 and R2 are known, or they can be prepared in a known manner, analogously to known compounds, for example based on Scheme 4. Alternatively, derivatizations can also be carried out at the stage of the compounds 3. Thus, using compounds where R2 = H, it is possible to prepare, for example, compounds where R2 = CH_2OH (by Vilsmaier reaction and subsequent reduction), where R2 = Cl or Br (by chlorination or bromination), where R2 = propynyl (from the corresponding bromine compound using the Sonogashira reaction) or where R2 = alkoxycarbonyl (from the corresponding bromine compound by Heck carbonylation).

The examples below serve to illustrate the invention in more detail without limiting it. Further compounds of the formula 1 whose preparation is not described explicitly can likewise be prepared in an analogous manner or in a manner known per to the person skilled in the art, using customary process techniques. The compounds named expressly as examples, and the salts of these compounds, are preferred subject matter of the invention. The abbreviation min stands for minute(s), h stands for hour(s) and m.p. stands for melting point.

Examples

1. (8*R*,9*R*)-2,3-Dimethyl-9-phenyl-8-pivaloyloxy-7,8,9,10-tetrahydroimidazo[1.2-h][1.7]naphthyridin-7-one

Under argon and with exclusion of moisture, 140 g of (8*R*,9*R*)-2,3-dimethyl-8-hydroxy-9-phenyl-7,8,9,10-tetrahydroimidazo[1.2-h][1.7]naphthyridin-7-one (WO 00/17200, Example B1) are suspended in 1100 ml of dichloromethane. 70 ml of triethylamine and 2.5 g of 4-dimethylaminopyridine are added, and a solution of 62 ml of pivaloyl chloride in 70 ml of dichloromethane is then added dropwise such that the temperature of the reaction mixture does not exceed 30°C (cooling with a water bath). The mixture is stirred overnight and then poured into 1 l of ice-water and stirred for another 10 min in the cold. The organic phase is separated off and the aqueous phase is extracted with dichloromethane (2 x 200 ml). The combined organic phases are washed with water (3 x 300 ml) until neutral, dried over sodium sulfate and evaporated. This gives 220 g of a yellowish oil which is crystallized using 600 ml of *tert*-butyl methyl ether. The mixture is stirred in the cold for 2 h and then filtered off, and the filter residue is washed with 200 ml of *tert*-butyl methyl ether and dried in a vacuum drying cabinet until the weight remains constant. This gives 175 g (97%) of the title compound as a slightly yellowish solid of m.p. 185-187°C.

2. (8*R*,9*R*)-10-Acetyl-2,3-dimethyl-9-phenyl-8-pivaloyloxy-7,8,9,10-tetrahydroimidazo[1.2-h]-[1.7]naphthyridin-7-one

Under argon and with exclusion of moisture, 175 g of (8*R*,9*R*)-2,3-dimethyl-9-phenyl-8-pivaloyloxy-7,8,9,10-tetrahydroimidazo[1.2-h][1.7]naphthyridin-7-one are dissolved with mechanical stirring in 2200 ml of toluene. With ice-cooling, half of the acetyl chloride (130 ml in total) is added dropwise over 30 min. The ice-bath is removed, and half of the triethylamine (250 ml in total) is added dropwise at 10°C over a period of 40 min (the temperature rises to up to 30°C). After 15 min at this temperature, the second half of the stated reagents is added as described above. With stirring, the mixture is then poured into 1 l of ice-water. The organic phase is separated off and the aqueous phase is extracted with ethyl acetate (2 x 200 ml). The combined organic phases are washed with water (3 x 400 ml), dried over sodium sulfate and evaporated. The yellow-brown residue is crystallized using 300 ml of *tert*-butyl methyl ether. After 1 h of stirring in the cold, the mixture is filtered off and the filter residue is washed with 200 ml of *tert*-butyl methyl ether and dried in a vacuum drying cabinet until the weight remains constant. 186 g (95%) of the title compound are isolated as a yellowish solid of m.p. 168-170°C.

3. (7*R*,8*R*,9*R*)-10-Acetyl-7-hydroxy-2,3-dimethyl-9-phenyl-8-pivaloyloxy-7,8,9,10-tetrahydroimidazo[1.2-h][1.7]naphthyridine

With mechanical stirring 165 g of (8*R*,9*R*)-10-acetyl-2,3-dimethyl-9-phenyl-8-pivaloyloxy-7,8,9,10-tetrahydroimidazo[1.2-h][1.7]naphthyridin-7-one are suspended in 2.0 l of isopropanol. With ice-cooling,

47.8 g of sodium cyanoborohydride are then introduced. 20 drops of Methyl Orange are added, and methanolic hydrogen chloride solution is then slowly added dropwise until the color remains red (about 150 ml, 1 h, warming of the reaction mixture to 16°C). After a further 20 min, the mixture is poured into 1.5 l of ice-water and 1 l of dichloromethane and neutralized with ammonia solution (25%). The organic phase is separated off and the aqueous phase is extracted with 250 ml of dichloromethane. The combined organic phases are re-extracted with water (3 x 1.5 l), dried over sodium sulfate and evaporated using a rotary evaporator. Coevaporation with acetone (3 x) and drying of the residue under high vacuum gives 160 g (90%) of the title compound as a colorless foam of m.p. 103-105°C which is used without further purification for the next step.

4. (7*R*,8*R*,9*R*)-10-Acetyl-7,8-dihydroxy-2,3-dimethyl-9-phenyl-7,8,9,10-tetrahydroimidazo-[1.2-h][1.7]naphthyridine

With stirring, 160 g of (7*R*,8*R*,9*R*)-10-acetyl-7-hydroxy-2,3-dimethyl-9-phenyl-8-pivaloyloxy-7,8,9,10-tetrahydroimidazo[1.2-h][1.7]naphthyridine are dissolved in 0.7 l of methanol, and 40 g of potassium carbonate are added. After about 10 min, the product begins to precipitate from the reaction mixture. After 1 h of stirring at room temperature, the mixture is poured into a solution of 200 g of ammonium chloride and 1.8 l of ice-water. The mixture is stirred for another 1 h at ice-bath temperature and the precipitated solid is then filtered off with suction and washed with a little methanol (80 ml). After drying in a vacuum cabinet at 50°C, 92.0 g (73%) of the title compound are isolated as a colorless solid of m.p. 260-261°C which is used without further purification for the next step. Alternatively, the title compound can also be prepared according to Examples 5 and 6.

5. (8*R*,9*R*)-8,10-Diacetyl-2,3-dimethyl-9-phenyl-7,8,9,10-tetrahydroimidazo[1.2-h][1.7]naphthyridin-7-one

Under nitrogen and with exclusion of moisture, 50 g of (8*R*,9*R*)-2,3-dimethyl-8-hydroxy-9-phenyl-7,8,9,10-tetrahydroimidazo[1.2-h][1.7]naphthyridin-7-one (WO 00/17200, Example B1) are dissolved in 450 ml of dichloromethane. At room temperature, initially half of the acetyl chloride (46.6 ml in total) is added dropwise. With ice-cooling, half of the triethylamine (45 ml in total) is then added dropwise over a period of 30 min. After 1 h of stirring at room temperature, the second half of the stated reagents is added as described. The mixture is then hydrolyzed using saturated sodium bicarbonate solution and water. The organic phase is separated off and the aqueous phase is extracted with dichloromethane. The combined organic phases are dried over magnesium sulfate and evaporated. The yellow-brown residue is coevaporated twice with toluene. 64 g of the title compound are isolated as a brown oil which is used without further purification for the next step.

6. (7*R*,8*R*,9*R*)-10-Acetyl-7,8-dihydroxy-2,3-dimethyl-9-phenyl-7,8,9,10-tetrahydro-imidazo[1.2-h][1.7]naphthyridine

64 g of (8*R*,9*R*)-8,10-diacetyl-2,3-dimethyl-9-phenyl-7,8,9,10-tetrahydroimidazo[1.2-h][1.7]naphthyridin-

7-one (crude product) are dissolved in 250 ml of methanol. With ice-cooling, 12.3 g of sodium borohydride are introduced. After 1 h of stirring, 23 g of potassium carbonate are added to the reaction mixture, which is then stirred at room temperature for another 2 h. The mixture is then poured into ice-water and the precipitate is filtered off with suction. The precipitate is washed with acetone and ether, and 37 g of the title compound are isolated.

7. (7*S*,8*R*,9*R*)-10-Acetyl-7,8-epoxy-2,3-dimethyl-7,8,9,10-tetrahydroimidazo[1.2-h][1.7]naphthyridine

Under nitrogen, with exclusion of moisture and with ice-cooling, 98.0 g of (7*R*,8*R*,9*R*)-10-acetyl-7,8-dihydroxy-2,3-dimethyl-9-phenyl-7,8,9,10-tetrahydroimidazo[1.2-h][1.7]naphthyridine are suspended in 720 ml of dichloromethane. 79 ml of tributyl phosphine are added, and 60 ml of diisopropyl azodicarboxylate are then added dropwise at an internal temperature of 5°C over a period of 45 min. After the addition has ended, the orange solution is stirred with ice-cooling for another 20 min. The reaction mixture is poured into 1 l of ice-water, the organic phase is separated off and the aqueous phase is extracted with dichloromethane (2 x 100 ml). The combined organic phases are washed with water (3 x 500 ml) and dried over sodium sulfate. When the organic phase is concentrated on a rotary evaporator (bath temperature < 40°C), the crystallization of the product starts when the volume has been reduced to about 1/10 of the original volume. With stirring, 500 ml of *tert*-butyl methyl ether are then slowly added dropwise. After 1 h of stirring with ice-cooling, the precipitate is filtered off with suction and washed with 200 ml of *tert*-butyl methyl ether. The product is dried at 40°C in a vacuum drying cabinet until the weight remains constant. 86.0 g (92%) of the title compound are isolated as a colorless solid of m.p. 205-206°C.

8. (7*S*,8*S*,9*R*)-8-Hydroxy-2,3,7-trimethyl-7,8,9,10-tetrahydroimidazo[1.2-h][1.7]naphthyridine

Under nitrogen, 3.75 ml of methylmagnesium bromide solution (3N in diethyl ether) are initially charged in 10 ml of tetrahydrofuran at -78°C. A solution of 1.5 g of (7*S*,8*R*,9*R*)-10-acetyl-7,8-epoxy-2,3-dimethyl-7,8,9,10-tetrahydroimidazo[1.2-h][1.7]naphthyridine in 10 ml of dichloromethane is then added dropwise over a period of 10 min. After 2 h, the reaction mixture is allowed to warm to 10°C and poured into 20 ml of water. After addition of 5 ml of saturated ammonium chloride solution, the mixture is extracted with dichloromethane and the organic phase is washed with water and evaporated. The residue is purified by silica gel chromatography (diethyl ether/triethylamine 4:1). Following crystallization from diethyl ether, 200 mg (15%) of the title compound are isolated as a colorless solid of m.p. > 240°C.

9. (7*S*,8*S*,9*R*)-7-Cyanomethyl-8-hydroxy-2,3-dimethyl-7,8,9,10-tetrahydroimidazo[1.2h]-[1.7]naphthyridine

Under nitrogen, 92 ml of lithium diisopropyldiamide solution (2 M) are initially charged at -78°C, and 9.7 ml of acetonitrile are added over a period of 30 min. After 1 h, a solution of 6 g of (7*S*,8*R*,9*R*)-10-

acetyl-7,8-epoxy-2,3-dimethyl-7,8,9,10-tetrahydroimidazo[1.2-h][1.7]naphthyridine in 30 ml of dichloromethane is added dropwise at -50°C over a period of 20 min. After 1 h at this temperature, the reaction mixture is allowed to warm to -20°C and poured into 200 ml of water. The pH is adjusted to 9 using saturated ammonium chloride solution, the mixture is extracted with ethyl acetate and the organic phase is washed with water. After evaporation, the residue is purified by silica gel chromatography (diethyl ether/triethylamine 9:1). Crystallization from acetonitrile gives 2.04 g (34%) of the title compound as a light-yellow solid of m.p. 214-216°C.

10. (7*S*,8*S*,9*R*)-8-Hydroxy-2,3-dimethyl-7-propyl-7,8,9,10-tetrahydroimidazo[1.2-h][1.7]naphthyridine

Starting with (7*S*,8*R*,9*R*)-10-Acetyl-7,8-epoxy-2,3-dimethyl-7,8,9,10-tetrahydroimidazo[1.2-h][1.7]naphthyridine and using propylmagnesium bromide, the title compound of m.p. 173-174°C is obtained analogously to example 8.

11. (7*R*,8*S*,9*R*)-8-Hydroxy-2,3-dimethyl-7-(3-methoxypropyl)-7,8,9,10-tetrahydroimidazo-[1.2-h][1.7]naphthyridine

Starting with (7*S*,8*R*,9*R*)-10-acetyl-7,8-epoxy-2,3-dimethyl-7,8,9,10-tetrahydroimidazo[1.2-h][1.7]-naphthyridine and using 3-methoxypropylmagnesium bromide, the title compound of m.p. 140-142°C is obtained analogously to example 8.

Commercial utility

The compounds of the formula 1 and their salts have valuable pharmacological properties which make them commercially utilizable. In particular, they exhibit marked inhibition of gastric acid secretion and an excellent gastric and intestinal protective action in warm-blooded animals, in particular humans. In this connection, the compounds according to the invention are distinguished by a high selectivity of action, an advantageous duration of action, a particularly good enteral activity, the absence of significant side effects and a large therapeutic range.

"Gastric and intestinal protection" in this connection is understood as meaning the prevention and treatment of gastrointestinal diseases, in particular of gastrointestinal inflammatory diseases and lesions (such as, for example, gastric ulcer, duodenal ulcer, gastritis, hyperacidic or medicament-related functional dyspepsia), which can be caused, for example, by microorganisms (e.g. Helicobacter pylori), bacterial toxins, medicaments (e.g. certain antiinflammatories and antirheumatics), chemicals (e.g. ethanol), gastric acid or stress situations.

In their excellent properties, the compounds according to the invention surprisingly prove to be clearly superior to the compounds known from the prior art in various models in which the antiulcerogenic and the antisecretory properties are determined. On account of these properties, the compounds of the formula 1 and their pharmacologically acceptable salts are outstandingly suitable for use in human and veterinary medicine, where they are used, in particular, for the treatment and/or prophylaxis of disorders of the stomach and/or intestine.

A further subject of the invention are therefore the compounds according to the invention for use in the treatment and/or prophylaxis of the abovementioned diseases.

The invention likewise includes the use of the compounds according to the invention for the production of medicaments which are employed for the treatment and/or prophylaxis of the abovementioned diseases.

The invention furthermore includes the use of the compounds according to the invention for the treatment and/or prophylaxis of the abovementioned diseases.

A further subject of the invention are medicaments which comprise one or more compounds of the formula 1 and/or their pharmacologically acceptable salts.

The medicaments are prepared by processes which are known per se and familiar to the person skilled in the art. As medicaments, the pharmacologically active compounds according to the invention (= active compounds) are either employed as such, or preferably in combination with suitable

pharmaceutical auxiliaries or excipients in the form of tablets, coated tablets, capsules, suppositories, patches (e.g. as TTS), emulsions, suspensions or solutions, the active compound content advantageously being between 0.1 and 95% and it being possible to obtain a pharmaceutical administration form exactly adapted to the active compound and/or to the desired onset and/or duration of action (e.g. a sustained-release form or an enteric form) by means of the appropriate selection of the auxiliaries and excipients.

The auxiliaries and excipients which are suitable for the desired pharmaceutical formulations are known to the person skilled in the art on the basis of his/her expert knowledge. In addition to solvents, gel-forming agents, suppository bases, tablet auxiliaries and other active compound excipients, it is possible to use, for example, antioxidants, dispersants, emulsifiers, antifoams, flavor corrigents, preservatives, solubilizers, colorants or, in particular, permeation promoters and complexing agents (e.g. cyclodextrins).

The active compounds can be administered orally, parenterally or percutaneously.

In general, it has proven advantageous in human medicine to administer the active compound(s) in the case of oral administration in a daily dose of approximately 0.01 to approximately 20, preferably 0.05 to 5, in particular 0.1 to 1.5, mg/kg of body weight, if appropriate in the form of several, preferably 1 to 4, individual doses to achieve the desired result. In the case of a parenteral treatment, similar or (in particular in the case of the intravenous administration of the active compounds), as a rule, lower doses can be used. The establishment of the optimal dose and manner of administration of the active compounds necessary in each case can easily be carried out by any person skilled in the art on the basis of his/her expert knowledge.

If the compounds according to the invention and/or their salts are to be used for the treatment of the abovementioned diseases, the pharmaceutical preparations can also contain one or more pharmacologically active constituents of other groups of medicaments, for example: tranquillizers (for example from the group of the benzodiazepines, for example diazepam), spasmolytics (for example, bietamiverine or camylofine), anticholinergics (for example, oxyphencyclimine or phencarbamide), local anesthetics (for example, tetracaine or procaine), and, if appropriate, also enzymes, vitamins or amino acids.

To be emphasized in this connection is in particular the combination of the compounds according to the invention with pharmaceuticals which inhibit acid secretion, such as, for example, H2 blockers (e.g. cimetidine, ranitidine), H^+/K^+ ATPase inhibitors (e.g. omeprazole, pantoprazole), or further with so-called peripheral anticholinergics (e.g. pirenzepine, telenzepine) and with gastrin antagonists with the aim of increasing the principal action in an additive or super-additive sense and/or of eliminating or of decreasing the side effects, or further the combination with antibacterially active substances (such as,

for example, cephalosporins, tetracyclines, penicillins, macrolides, nitroimidazoles or alternatively bismuth salts) for the control of Helicobacter pylori. Suitable antibacterial co-components which may be mentioned are, for example, mezlocillin, ampicillin, amoxicillin, cefalothin, cefoxitin, cefotaxime, imipenem, gentamycin, amikacin, erythromycin, ciprofloxacin, metronidazole, clarithromycin, azithromycin and combinations thereof (for example clarithromycin + metronidazole).

Pharmacology

The excellent gastric protective action and the gastric acid secretion-inhibiting action of the compounds according to the invention can be demonstrated in investigations on animal experimental models. The compounds according to the invention investigated in the model mentioned below have been provided with numbers which correspond to the numbers of these compounds in the examples.

Testing of the secretion-inhibiting action on the perfused rat stomach

In Table A which follows, the influence of the compounds according to the invention on the pentagastrin-stimulated acid secretion of the perfused rat stomach after intraduodenal administration in vivo is shown.

Table A

No.	Dose (μmol/kg) i.d.	Inhibition of acid secretion (%)
8	1	93
9	0.3	52

Methodology

The abdomen of anesthetized rats (CD rat, female, 200-250 g; 1.5 g/kg i.m. urethane) was opened after tracheotomy by a median upper abdominal incision and a PVC catheter was fixed transorally in the esophagus and another via the pylorus such that the ends of the tube just projected into the gastric lumen. The catheter leading from the pylorus led outward into the right abdominal wall through a side opening.

After thorough rinsing (about 50-100 ml), warm (37°C) physiological NaCl solution was continuously passed through the stomach (0.5 ml/min, pH 6.8-6.9; Braun-Unita I). The pH (pH meter 632, glass electrode EA 147; ϕ = 5 mm, Metrohm) and, by titration with a freshly prepared 0.01 N NaOH solution to pH 7 (Dosimat 665 Metrohm), the secreted HCl were determined in the effluent in each case collected at an interval of 15 minutes.

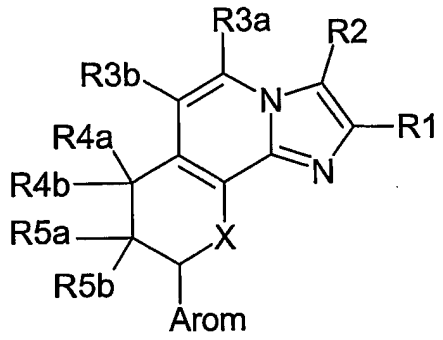
The gastric secretion was stimulated by continuous infusion of 1 μg/kg (= 1.65 ml/h) of i.v. pentagastrin (left femoral vein) about 30 min after the end of the operation (i.e. after determination of 2 preliminary

fractions). The substances to be tested were administered intraduodenally in a 2.5 ml/kg liquid volume 60 min after the start of the continuous pentagastrin infusion.

The body temperature of the animals was kept at a constant 37.8-38°C by infrared irradiation and heat pads (automatic, stepless control by means of a rectal temperature sensor).

We claim:

1. A compound of the formula 1



(1)

where

R1 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxycarbonyl, 2-4C-alkenyl, 2-4C-alkynyl, fluoro-1-4C-alkyl or hydroxy-1-4C-alkyl,

R2 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, 1-4C-alkoxycarbonyl, hydroxy-1-4C-alkyl, halogen, 2-4C-alkenyl, 2-4C-alkynyl, fluoro-1-4C-alkyl or cyanomethyl,

R3a is hydrogen, halogen, fluoro-1-4C-alkyl, 1-4C-alkyl, 2-4C-alkenyl, 2-4C-alkynyl, 1-4C-alkoxy, carboxyl, 1-4C-alkoxycarbonyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkyl, fluoro-1-4C-alkoxy-1-4C-alkyl or the radical -CO-NR31R32,

R3b is hydrogen, halogen, fluoro-1-4C-alkyl, 1-4C-alkyl, 2-4C-alkenyl, 2-4C-alkynyl, 1-4C-alkoxy, carboxyl, 1-4C-alkoxycarbonyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkoxy-1-4C-alkoxy-1-4C-alkyl, fluoro-1-4C-alkoxy-1-4C-alkyl or the radical -CO-NR31R32,

where

R31 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl and

R32 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl,

or where

R31 and R32 together and including the nitrogen atom to which they are attached form a pyrrolidino, piperidino or morpholino radical,

one of the substituents R4a and R4b is hydrogen and the other is the radical R41,

where

R41 is 1-7C-alkyl, 2-7C-alkenyl, 3-7C-cycloalkyl, 1-4C-alkoxy-1-4C-alkyl, cyano-1-4C-alkyl, phenyl or phenyl-1-4C-alkyl,

one of the substituents R5a and R5b is hydrogen and the other is hydroxyl, 1-4C-alkoxy, oxo-substituted 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkyl-1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, 3-7C-cycloalkoxy-1-4C-alkoxy, 3-7C-cycloalkyl-1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkylcarbonyloxy, fully or predominantly halogen-substituted 1-4C-alkoxy or the radical R51,

where

R51 is a radical which, under physiological conditions, forms a hydroxyl group,

Arom is a R8-, R9-, R10- and R11-substituted mono- or bicyclic aromatic radical selected from the group consisting of phenyl, naphthyl, pyrrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, indolyl,

benzimidazolyl, furanyl (furyl), benzofuranyl (benzofuryl), thiophenyl (thienyl), benzothiophenyl (benzothienyl), thiazolyl, isoxazolyl, pyridinyl, pyrimidinyl, quinolinyl and isoquinolinyl,

where

R8 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy, 2-4C-alkenyloxy, 1-4C-alkylcarbonyl, carboxyl, 1-4C-alkoxycarbonyl, carboxy-1-4C-alkyl, 1-4C-alkoxycarbonyl-1-4C-alkyl, halogen, hydroxyl, aryl, aryl-1-4C-alkyl, aryloxy, aryl-1-4C-alkoxy, trifluoromethyl, nitro, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or sulfonyl,

R9 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxyl,

R10 is hydrogen, 1-4C-alkyl or halogen and

R11 is hydrogen, 1-4C-alkyl or halogen,

where

aryl is phenyl or substituted phenyl having one, two or three identical or different substituents from the group consisting of 1-4C-alkyl, 1-4C-alkoxy, carboxyl, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl, nitro, trifluoromethoxy, hydroxyl and cyano,

X is O (oxygen) or NH,

and its salts.

2. A compound of the formula 1 as claimed in claim 1, where

R1 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl, 1-4C-alkoxy-1-4C-alkyl, 2-4C-alkynyl or fluoro-1-4C-alkyl,

R2 is hydrogen, 1-4C-alkyl, halogen, 2-4C-alkenyl, 2-4C-alkynyl or fluoro-1-4C-alkyl,

R3a is hydrogen,

R3b is hydrogen, halogen, 1-4C-alkyl or the radical -CO-NR31R32,

where

R31 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl and

R32 is hydrogen, 1-7C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxy-1-4C-alkyl,

or where

R31 and R32 together and including the nitrogen atom to which they are attached are a pyrrolidino, piperidino or morpholino radical,

one of the substituents R4a and R4b is hydrogen and the other is the radical R41,

where

R41 is 1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, cyano-1-4C-alkyl or phenyl-1-4C-alkyl,

one of the substituents R5a and R5b is hydrogen and the other is hydroxyl, 1-4C-alkoxy, oxo-substituted 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkyl-1-4C-alkoxy or 1-4C-alkoxy-1-4C-alkoxy,

Arom is a R8-, R9-, R10- and R11-substituted mono- or bicyclic aromatic radical selected from the group consisting of phenyl, furanyl (furyl) and thiophenyl (thienyl),

where

R8 is hydrogen, 1-4C-alkyl, hydroxy-1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkylcarbonyl, carboxyl, 1-4C-alkoxycarbonyl, halogen, hydroxyl, trifluoromethyl, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonylamino, 1-4C-alkoxy-1-4C-alkoxycarbonylamino or sulfonyl,

R9 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, halogen, trifluoromethyl or hydroxyl,

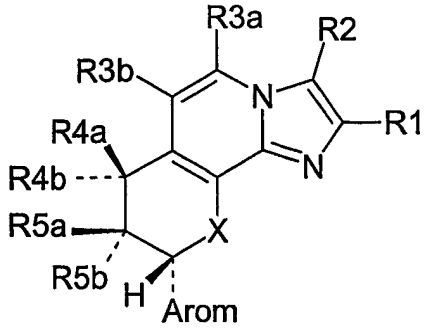
R10 is hydrogen and

R11 is hydrogen,

X is O (oxygen) or NH,

and its salts.

3. A compound as claimed in claim 1, characterized by the formula 1*



(1*)

where

R1 is hydrogen, methyl, cyclopropyl, methoxymethyl or trifluoromethyl,

R2 is hydrogen, methyl, chlorine, bromine, ethynyl or trifluoromethyl,

R3a is hydrogen,

R3b is hydrogen, fluorine, methyl or the radical -CO-N(CH_3)$_2$,

one of the substituents R4a and R4b is hydrogen and the other is the radical R41, where

R41 is 1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, cyano-1-4C-alkyl or phenyl-1-4C-alkyl

one of the substituents R5a and R5b is hydrogen and the other is hydroxyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, methoxyethoxy, methoxypropoxy, methoxyethoxyethoxy, 2-oxopropoxy, cyclopropyloxy or cyclopropylmethoxy,

Arom is a phenyl radical,

X is O (oxygen) or NH,

and its salts.

4. A compound as claimed in claim 1 of the formula 1* as claimed in claim 3, where

R1 is 1-4C-alkyl,

R2 is 1-4C-alkyl,

R3a is hydrogen,

R3b is hydrogen,

one of the substituents R4a and R4b is hydrogen and the other is the radical R41, where

R41 is 1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, cyano-1-4C-alkyl or phenyl-1-4C-alkyl,

one of the substituents R5a and R5b is hydrogen and the other is hydroxyl,

Arom is a phenyl radical,
X is O (oxygen) or NH,
and its salts.

5. A compound as claimed in claim 1 of the formula 1* as claimed in claim 3, where
R1 is 1-4C-alkyl,
R2 is 1-4C-alkyl,
R3a is hydrogen,
R3b is hydrogen,
one of the substituents R4a and R4b is hydrogen and the other is the radical R41, where
R41 is 1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl or cyano-1-4C-alkyl,
R5a is hydroxyl,
R5b is hydrogen,
Arom is a phenyl radical,
X is O (oxygen) or NH,
and its salts.

6. A medicament comprising a compound as claimed in claim 1 and/or a pharmacologically acceptable salt thereof together with customary pharmaceutical auxiliaries and/or excipients.

7. The use of compounds as claimed in claim 1 and their pharmacologically acceptable salts for the prevention and treatment of gastrointestinal disorders.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/08498

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/14 A61K31/435 C07D491/14 A61P1/04 A61K31/35
//(C07D471/14,235:00,221:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 54188 A (BYK GULDEN LOMBERG CHEM FAB ;SENN BILFINGER JOERG (DE)) 3 December 1998 (1998-12-03) cited in the application * siehe die Definition von R4a, R4b * the whole document ---	1-7
Y	WO 98 42707 A (BYK GULDEN LOMBERG CHEM FAB ;GRUNDLER GERHARD (DE); SENN BILFINGER) 1 October 1998 (1998-10-01) cited in the application * siehe die Definition von R4a, R4b * the whole document --- -/--	1-7

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 December 2002	20/12/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Stellmach, J

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 00 17200 A (BYK GULDEN LOMBERG CHEM FAB ;SENN BILFINGER JOERG (DE)) 30 March 2000 (2000-03-30) cited in the application * siehe die Definition von R2a, R2b * the whole document	1-7
Y	WO 00 63211 A (BYK GULDEN LOMBERG CHEM FAB ;SENN BILFINGER JOERG (DE)) 26 October 2000 (2000-10-26) cited in the application * siehe die Definition von R4a, R4b * the whole document	1-7
Y	WO 95 27714 A (ASTRA AB ;BRIVING CARIN BIRGITTA (SE); NORDBERG MATS PETER (SE); S) 19 October 1995 (1995-10-19) * siehe Ansprüche 1-8 * the whole document	1-7
Y	US 4 468 400 A (GOLD ELIJAH H ET AL) 28 August 1984 (1984-08-28) cited in the application * siehe Ansprüche 1-11 * the whole document	1-7
Y	KAMINSKI J J ET AL: "ANTIULCER AGENTS. 5. INHIBITION OF GASTRIC H+/K+-ATPASE BY SUBSITUTED IMIDAZOL1,2-A PYRIDINES AND RELATED ANALOGUES AND ITS IMPLICATION IN MODELING THE HIGH AFFINITY POTASSIUM ION BINDING SITE OF THE GASTRIC PROTON PUMP ENZYME" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 34, 1991, pages 533-541, XP000919185 ISSN: 0022-2623 * siehe S. 534, Fig. 7 * the whole document	1-7
Y	KAMINSKI J J ET AL: "ANTIULCER AGENTS. 6. ANALYSIS OF THE IN VITRO BIOCHEMICAL AND IN VIVO GASTRIC ANTISECRETORY ACTIVITY OF SUBSTITUTE IMIDAZO1,2-A PYRIDINES AND RELATED ANALOGUES USING COMPARATIVE MOLECULAR FIELD ANALYSIS AND HYPOTHETICAL ACTIVE SITE LATTICE METHODOLOGIES" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 40, 1997, pages 427-436, XP000941533 ISSN: 0022-2623 * siehe S. 428, Tab. 1 * the whole document	1-7

-/--

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/08498

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 01 72754 A (SIMON WOLFGANG ALEXANDER;BYK GULDEN LOMBERG CHEM FAB ; BUHR WILM () 4 October 2001 (2001-10-04) * siehe Ansprüche 1-6 * the whole document	1-7
P,X	WO 01 72757 A (BYK GULDEN LOMBERG CHEM FAB ;BUHR WILM (DE); STURM ERNST (DE); HUB) 4 October 2001 (2001-10-04) * siehe Ansprüche 1-9 * the whole document	1-7

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9854188	A	03-12-1998	AU	736767 B2	02-08-2001
			AU	7915498 A	30-12-1998
			BR	9809185 A	01-08-2000
			CN	1257505 T	21-06-2000
			WO	9854188 A1	03-12-1998
			EP	0984969 A1	15-03-2000
			JP	2001526703 T	18-12-2001
			US	6160119 A	12-12-2000
			ZA	9804463 A	30-11-1998
WO 9842707	A	01-10-1998	AU	740578 B2	08-11-2001
			AU	7520898 A	20-10-1998
			BG	103696 A	30-06-2000
			BR	9807883 A	22-02-2000
			CN	1251102 T	19-04-2000
			CZ	9903397 A3	12-04-2000
			EA	2402 B1	25-04-2002
			EE	9900450 A	17-04-2000
			WO	9842707 A1	01-10-1998
			EP	0971922 A1	19-01-2000
			HR	980147 A1	28-02-1999
			HU	0001555 A2	28-11-2000
			JP	2001518098 T	09-10-2001
			NO	994584 A	23-11-1999
			NZ	337325 A	29-06-2001
			PL	335699 A1	08-05-2000
			SK	129799 A3	16-05-2000
			TR	9902257 T2	21-12-1999
			US	6197783 B1	06-03-2001
WO 0017200	A	30-03-2000	AU	6192099 A	10-04-2000
			BG	105270 A	30-11-2001
			BR	9914044 A	04-12-2001
			CA	2344251 A1	30-03-2000
			CN	1319101 T	24-10-2001
			CZ	20011082 A3	12-09-2001
			EE	200100172 A	17-06-2002
			WO	0017200 A1	30-03-2000
			EP	1115725 A1	18-07-2001
			HR	20010224 A1	30-04-2002
			HU	0102990 A2	28-01-2002
			JP	2002526499 T	20-08-2002
			NO	20011243 A	12-03-2001
			PL	346617 A1	25-02-2002
			SK	3992001 A3	03-12-2001
			TR	200100805 T2	21-08-2001
			US	2002169320 A1	14-11-2002
			US	6436953 B1	20-08-2002
WO 0063211	A	26-10-2000	AU	3966600 A	02-11-2000
			WO	0063211 A1	26-10-2000
			EP	1173439 A1	23-01-2002
WO 9527714	A	19-10-1995	AU	2270695 A	30-10-1995
			WO	9527714 A1	19-10-1995
			ZA	9502860 A	12-01-1996
US 4468400	A	28-08-1984	NONE		

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0172754 A	04-10-2001	AU 4422501 A	08-10-2001
		WO 0172754 A1	04-10-2001
		NO 20024597 A	25-09-2002
WO 0172757 A	04-10-2001	AU 5475601 A	08-10-2001
		WO 0172757 A1	04-10-2001